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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,256	10/29/2003	Neal I. Azrolan	AM-100302C1USA	7071

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EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,256	AZROLAN ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/16/04 & 1/22/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-27 ARE PRESENTED FOR EXAMINATION

Applicants' Preliminary Amendments filed October 29, 2003 and December 9, 2003 (including a supplemental Application Data Sheet) and Information Disclosure Statements filed January 22, 2004 and June 16, 2004 have been received and entered into the application.

Accordingly, the specification at pages 1 (twice amended) and 3 has been amended and claims 28-39 have been canceled. Also, as reflected by the attached, completed copies of "Substitute for form 1449/PTO", the Examiner has considered the cited references.

Specification

The specification is objected to because of the following informality. Appropriate correction is required.

In Applicants' Preliminary Amendment dated December 9, 2003, in which the specification at page 1 has been amended, --- now U.S. Patent No. 6,670,355--- should be inserted after "filed December 6, 2002," and ---now abandoned--- should be inserted after "filed June 13, 2001,---.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by either Morris et al. (U.S. Patent No. 5,516,781, cited by Applicants, reference "TT") or Mitchell et al.

(U.S. Patent No. 5,288,711, cited by Applicants, reference "Z") who teach methods for the treatment of hyperproliferative vascular disease in a mammal (see the abstract of either patent) which comprises the administration of rapamycin (see claims 2 and 9) alone (Morris et al., last two lines of the abstract) or rapamycin and heparin (Mitchell et al., last line of the abstract) [this is taken to meet the claim elements of treating or inhibiting cardiovascular disease in a mammal comprising providing said mammal with an effective amount of rapamycin (claim 1)]. Mitchell et al. further teaches that vascular injury, including injury attributed to autoimmune disorders or alloimmune related disorders or atherosclerosis may be treated (col. 3, lines 38-40 and 43) [taken to meet the claim elements of cardiovascular disease, peripheral vascular disease, atherosclerosis as well as "vascular wall damage from cellular events leading toward immune mediated vascular damage" (claims 1 and 8)]. Morris et al. also disclose that atherosclerosis may be treated (col. 1, lines 45-60; compare to claim 8). Also, because both references refer to "vascular" in general, such is deemed a sufficient disclosure to have placed vascular disease, whether it is peripheral (see present claim 8) or central, in the possession of the public.

Steadman's Medical Dictionary (cited by the Examiner) defines atherosclerosis to mean "arteriosclerosis characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries; such deposits are associated with fibrosis and calcification" (page 148, col. 1). Therefore, the references' disclosure of atherosclerosis is deemed to have placed the concepts of "arteriosclerosis" (claim 8) in the possession of the public.

The additional reference, i.e., Stedman's Medical Dictionary, is relied on to explain the meaning of a term used in the primary reference. "Normally, only one reference should be used

in making a rejection under 35 U.S.C. § 102. However, a 35 U.S.C. § 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"

(B) Explain the meaning of a term used in the primary reference; or

(C) Show that a characteristic not disclosed in the reference is inherent." (See MPEP § 2131.01). Accordingly, the Examiner's reliance on the additional reference is proper.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al. (U.S. Patent No. 5,516,781, cited by Applicants, reference "TT") or Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z"), as relied on above, in view of Wright et al.

(U.S. Patent No. 6,585,764, cited by the Examiner), Schuler et al. (U.S. Patent No. 6,384,046), Somers (U.S. Patent No. 6,121,319, cited by Applicants, reference "XX"), Applicants' acknowledgment at page 5, line 10 – page 6, line 22 of the present specification and The Merck Manual of Diagnosis and Therapy ("Merck", cited by Applicants, reference "OOO").

The differences between the above and the claimed subject matter lies in that neither Morris et al. nor Mitchell et al. disclose:

(i) the presently claimed rapamycin derivatives as being useful in the place of rapamycin;

(ii) the additional use of the pharmaceutical agents of present claims 7, 14 or 21; and

(iii) the inhibition of stroke, multiinfarct dementia (present claim 15), treatment of coronary artery disease (present claim 1) or accumulation of lipid in a vascular wall (present claim 22).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) One of ordinary skill in the art concerned with the treatment of hyperproliferative vascular diseases would have been aware of not only Morris et al. or Mitchell et al., but of Schuler et al. as well. Schuler et al. disclose treatments for hyperproliferative vascular diseases, including atherosclerosis, wherein rapamycin derivatives are effectively employed (see Schuler et al. at the abstract; col. 1, line 5 – col. 2, line 36, col. 3, lines 41-46). Given the combined teaches of Morris et al. or Mitchell et al. and Schuler et al., it is believed that one of ordinary skill in the art would have been imbued with a reasonable expectation that not only could

rapamycin be administered, but rapamycin derivatives as well. One of such skill would have been motivated to employ the presently claimed rapamycin derivatives because from Applicants' acknowledgment at page 5, line 10 – page 6, line 22 of the present specification, such derivatives were known to the skilled artisan and as such, would have been expected to provide at least similar results to those achieved for rapamycin itself.

(ii) Somers et al. teach that the pharmaceutical agents of present claims 7, 14 or 21 were known to be useful for treating vascular diseases such as those of the primary references (see col. 6, lines 28-29 and col. 8, line 62 – col. 9, line 6) and it has been held that it is considered prima facie obvious to have combined two or more ingredients each of which was known to be useful for the same purpose in order to form a third composition that is useful for the very same purpose. The idea for combining them flows logically from their have been used separately. See *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980) and the cases cited therein. The skilled artisan would have been motivated to combine such ingredients in order to achieve *at least* additive results and to provide the individual being treated with the most convenient, effective therapy possible.

(iii) As discussed above, Morris et al. teach that rapamycin can treat hyperproliferative vascular disease, including atherosclerosis. Such disease includes the migration and proliferation of vascular smooth muscle cells and such plays a "crucial role in the pathogenesis of atherosclerosis" (see Morris et al. at col. 1, lines 49-51). Morris et al. further teach that atherosclerotic lesions include massive accumulation of *lipid laden* foam cells derived from monocyte/macrophage and smooth muscle cells (col. 1, lines 51-53). Accordingly, one of ordinary skill in the art would have recognized that because rapamycin was effective in the

treatment of atherosclerosis, it would also be effective for inhibiting or treating lipid deposition or accumulation in a vascular wall because atherosclerosis is characterized by lipid accumulation.

Respecting the treatment of stroke or multiinfarct dementia, Merck teaches that cerebrovascular disease, including ischemic syndromes, i.e., strokes (page 1324, col. 1) and transient ischemic attacks ("TIAs") (page 1324, col. 2, last section – page 1327) were known to have a causal association with hyperproliferative vascular diseases, i.e., caused by "thrombosis or emboli from an atherosclerotic plaque..." (page 1324, col. 1, lines 7-8 under the heading "Etiology and Pathophysiology"). Merck further teaches that "Most TIAs are due to cerebral emboli arising from plaques or atherosclerotic ulcers involving the carotid or vertebral arteries in the neck." (page 1326, col. 1, lines 1-3). Therefor, the inhibition or treatment for atherosclerosis would have been recognized as also being an effective inhibition for the development of a stroke. Also, regarding multiinfarct dementia, because it involves multiple infarcts and an "infarct" is an element of a stroke (Merck at page 1325, lines 1-2), it would have also been obvious that the development of multiinfarct dementia could also be inhibited.

Respecting the treatment or inhibition of coronary artery disease, such would have been obvious to one of ordinary skill in the art because this disease was known to have atherosclerosis as a component thereof, i.e., Wright et al. teach "Coronary heart disease is a major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000-600,000 deaths in the United States annually." (col. 2, lines 7-13). It is

believed that as a matter of interpretation, one could have considered an inhibition of or treatment for a component of a disease, i.e., inhibition of or treatment for atherosclerosis with rapamycin, as an inhibition of or treatment of the disease itself.

Accordingly, for the above reasons, the claims are deemed properly rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Non-Provisional

I Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,670,355, (cited by Applicants, reference "HHH") which has a common inventor and assignee with the present application.

Although the conflicting claims are not identical, they are not patentably distinct from each other because, as evident from the terms "coronary" and "syndrome", the "acute coronary syndrome" of patented claim 1 would have been recognized as a species of the presently claimed cardiovascular disease and thus the presently claimed subject matter would have been obvious to one of ordinary skill in the art from the teaching of the patent claims.

It is noted that the patented claims fail to include a step of administering any one of the additional active agents of present claim 7. However, because in the management of acute coronary syndrome, the artisan would have appreciated that therapy therefor which included combinations of active agents, including such agents as anticoagulants, was known (see Mruk, U.S. Patent No. 6,559,133, at, for example, the abstract), the artisan would have been motivated to use such combination therapy in order to provide the most effective therapy as possible to the patient.

II Claims 1, 7, 8, 14 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,680,330, (Zhu et al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z").

The differences between the present claims and the patented claims lies in that restenosis is being treated or inhibited in the patented claims with a dialdehyde rapamycin compound, while the present claims do not expressly set forth either a dialdehyde rapamycin compound or restenosis as a therapeutic objective.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims recite "a rapamycin" and thus includes rapamycin compounds in general which would have included the aldehyde derivative form of rapamycin of the patented claims. Also, the present claims recite the treatment or inhibition of cardiovascular disease or the treatment of atherosclerosis in general and would have included a treatment for restenosis because the defining characteristics of restenosis clearly indicate that it may be

considered a type of cardiovascular disease which may be associated with atherosclerosis and thus, the treatment of restenosis would be included in the scope of the present claims. In particular, Wright et al. (U.S. Patent No. 6,585,764), teaches the following regarding the characteristics of restenosis: "Re-narrowing [restenosis] of an atherosclerotic coronary artery after percutaneous angioplasty (PTCA) occurs in 10-50% of patient undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft." (col. 1, lines 23-27).

Present claim 22 requires that lipid deposition or accumulation be treated or inhibited. This requirement is believed to be met by the patented claims because restenosis occurs in a vessel that may be atherosclerotic, which would indicate that lipid accumulation in the vessel walls would be present (see Mitchell et al. at col. 1, lines 58-68). While the treatment of restenosis does not directly involve the lipid deposits, such deposits would indirectly be "treated" through the treatment of the restenosis thus meeting the present claim requirement.

It is noted that the patented claims also fail to include a step of administering any one of the additional active agents of present claims 7 or 14. However, the art was aware of successful instances of combination therapy for the treatment of restenosis, including combinations which included rapamycin and heparin, e.g., an anticoagulant, (see Mitchell et al., U.S. Patent No. 5,288,711, the abstract and col. 2, lines 15-31) and the artisan would have been motivated to employ active agents in addition to the rapamycin compound of the primary reference in order to provide the most effective therapy possible.

III Claims 1, 3, 4, 7, 8, 10, 11, 14, 22, 24 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of U.S.

Patent No. 6,432,973, (Zhu et al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z").

The differences between the present claims and the patented claims lies in that restenosis is being treated or inhibited in the patented claims with a rapamycin ester compound, while the present claims do not expressly set forth restenosis as a therapeutic objective.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims recite the treatment or inhibition of cardiovascular disease or the treatment of atherosclerosis in general and would have included a treatment for restenosis because the defining characteristics of restenosis clearly indicate that it may be considered a type of cardiovascular disease which may be associated with atherosclerosis and thus, the treatment of restenosis would be included in the scope of the present claims. In particular, Wright et al. (U.S. Patent No. 6,585,764), teaches the following regarding the characteristics of restenosis: "Re-narrowing [restenosis] of an atherosclerotic coronary artery after percutaneous angioplasty (PTCA) occurs in 10-50% of patient undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft." (col. 1, lines 23-27).

Present claim 22 requires that lipid deposition or accumulation be treated or inhibited. This requirement is believed to be met by the patented claims because restenosis occurs in a vessel that may be atherosclerotic, which would indicate that lipid accumulation in the vessel walls would be present (see Mitchell et al. at col. 1, lines 58-68). While the treatment of restenosis does not directly involve the lipid deposits, such deposits would indirectly be "treated" through the treatment of the restenosis thus meeting the present claim requirement.

It is noted that the patented claims also fail to include a step of administering any one of the additional active agents of present claims 7 or 14. However, the art was aware of successful instances of combination therapy for the treatment of restenosis, including combinations which included rapamycin and heparin, e.g., an anticoagulant, (see Mitchell et al., U.S. Patent No. 5,288,711, the abstract and col. 2, lines 15-31) and the artisan would have been motivated to employ active agents in addition to the rapamycin compound of the primary reference in order to provide the most effective therapy possible.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

April 20, 2005